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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
DAVIS, MINH TAM B	

ART UNIT	PAPER NUMBER
1642	

DATE MAILED: 09/15/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/069,973	GRIMM ET AL.	
	Examiner	Art Unit	
	MINH-TAM DAVIS	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 August 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *63-93* is/are pending in the application.

4a) Of the above claim(s) *66-68 and 76-93* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *63-65 and 69-75* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Applicant's election with traverse of group IV, claims 63-65, 69-75 in the response of 08/03/05 is acknowledged.

The traverse is on the following ground:

Applicant argues that the technical feature of all groups represent a contribution over the art.

Applicant argues that Fulda et al does not contain any indication that bongkreric acid is an inhibitor of ANT-1, and that the inhibition of ANT-1 leads to the inhibition of apoptosis, particularly in degenerative diseases like cardiomyopathy.

Applicant further argues that one had no reasons to suspect that the apoptosis inducers used by Fulda et al, doxorubicin and betulinic acid, were involved in the development of degenerative diseases, in particular cardiomyopathy.

The arguments are not found to be persuasive for the following reasons:

Bongkreric acid is inherently an inhibitor of ANT-1, in view of the teaching of Pei et al. In addition, exposure a neuroblastoma cell to bongkreric acid results in inhibition of apoptosis, as taught by Fulda et al.

Further, the limitation of degenerative diseases or cardiomyopathy is not recited in claim 63.

Clearly the shared technical feature is not a contribution over the prior art (see 102 rejection below), and thus unity does not exist, according to PCT Rule 13.2.

The requirement is still deemed proper and is therefore made FINAL.

After review and reconsideration, claim 74, however, is rejoined with group IV.

Accordingly, group IV, claims 63-65, 69-75, directed to a method for inhibition of apoptosis, or treating a disease associated with excessive apoptosis, wherein said disease is a degenerative disease, and wherein said degenerative disease is dilated cardiomyopathy, comprising inhibition of the activity of adenine nucleotide translocase-1 (ANT-1) on the protein level, are examined in the instant application.

INFORMATION DISCLOSURE STATEMENT

It is noted that the information disclosure statement of 03/11/02 could not be considered, because it is prior to the filing date of 06/17/02, and therefore has not been filed in this case.

REJECTION UNDER 35 USC 112, FIRST PARAGRAPH, WRITTEN DESCRIPTION

The instant specification does not contain a written description of the invention in such full, clear, concise, and exact terms or in sufficient detail that one skilled in the art can reasonably conclude that applicant had possession of the claimed invention at the time of filing.

Claims 63-65, 69-70, 72-75 are rejected under 35 USC 112, first paragraph, as lacking an adequate written description in the specification.

Claims 63-65, 69-70, 72-75 are drawn to:

1) A method for inhibition of apoptosis in a cell that could be associated with a pathogenic disorder, or treating diseases associated with excessive apoptosis, wherein the disease is a degenerative disease, and wherein said degenerative disease is dilated

cardiomyopathy, comprising administering "a substance capable of inhibiting the activity of adenine nucleotide translocase-1 (ANT-1), or ANT-1 protein antagonists" (claims 63-65, 69-70, 73-75).

2) The method of claim 63, wherein an apoptosis-inducing signal transduction pathway is inhibited, said pathway being activated by ANT-1 (claim 72).

The specification discloses that cyclophilin D, a component of the PT pore which directly interacts with ANT-1, and bongkrekic acid, a specific inhibitor of the PT pore, both repress apoptosis induced by ANT-1 in a cell line (p.15, item 2.5, and figure 7 on page 9).

The specification discloses that ANT-1 mediated apoptosis induction depends on protein-protein interactions that are specific for mammalian cells. The specification further discloses that the apoptosis induction by ANT-1 does not depends on its known function for ADP/ATP exchange, and is also independent of BAX-mediated apoptosis (p.2, last paragraph, brdinging p.3, first paragraph).

Which protein-protein interaction by ANT-1 leading to apoptosis however is not disclosed.

Similarly, **which apoptosis-inducing signal transduction pathway activated by ANT-1, and which proteins involved in the pathway are not disclosed.**

It is noted that **"a substance capable of inhibiting the activity of adenine nucleotide translocase-1 (ANT-1), or ANT-1 protein antagonists" encompasses both direct and indirect inhibitors of ANT-1, with diverse and unknown structure,** such as mimetics or small molecule inhibitors of ANT-1, or molecules that interfere with

of adenine nucleotide translocase-1 (ANT-1), or ANT-1 protein antagonists" (claims 63-65, 69-70, 73-75).

2) The method of claim 63, wherein an apoptosis-inducing signal transduction pathway is inhibited, said pathway being activated by ANT-1 (claim 72).

The specification discloses that cyclophilin D, a component of the PT pore which directly interacts with ANT-1, and bongkrekic acid, a specific inhibitor of the PT pore, both repress apoptosis induced by ANT-1 in a cell line (p.15, item 2.5, and figure 7 on page 9).

The specification discloses that ANT-1 mediated apoptosis induction depends on protein-protein interactions that are specific for mammalian cells. The specification further discloses that the apoptosis induction by ANT-1 does not depends on its known function for ADP/ATP exchange, and is also independent of BAX-mediated apoptosis (p.2, last paragraph, brdinging p.3, first paragraph).

Which protein-protein interaction by ANT-1 leading to apoptosis however is not disclosed.

Similarly, **which apoptosis-inducing signal transduction pathway activated by ANT-1, and which proteins involved in the pathway are not disclosed.**

It is noted that **"a substance capable of inhibiting the activity of adenine nucleotide translocase-1 (ANT-1), or ANT-1 protein antagonists" encompasses both direct and indirect inhibitors of ANT-1, with diverse and unknown structure**, such as mimetics or small molecule inhibitors of ANT-1, or molecules that interfere with

the protein-protein interaction by ANT-1 leading to apoptosis, or with the apoptosis-inducing signal pathway being activated by ANT-1.

In addition, **the recited ANT-1 without being accompanied by a sequence identification number encompasses variants ANT-1 with unknown structure.**

It is noted that although the specification discloses that the N-terminal half of ANT-1 is sufficient for apoptosis induction (p.13, item 2.2), the encompassed variant ANT-1 could have any deletion, substitution or addition at any amino acids throughout the entire length of the ANT-1 protein.

Although drawn to DNA arts, the findings in University of California v. Eli Lilly and Co., 119 F.3d 1559, 43 USPQ2d 1398 (Fed. Cir. 1997) and Enzo Biochem, Inc. V. Gen-Probe Inc. are relevant to the instant claims. The Federal Circuit addressed the application of the written description requirement to DNA-related inventions in University of California v. Eli Lilly and Co., 119 F.3d 1559, 43 USPQ2d 1398 (Fed. Cir. 1997). The court stated that "[a] written description of an invention involving a chemical genus, like a description of a chemical species, requires a precise definition, such as by structure, formula, [or] chemical name," of the claimed subject matter sufficient to distinguish it from other materials. Id. At 1567, 43 USPQ2d at 1405. The court also stated that

> a generic statement such as "vertebrate insulin cDNA" or "mammalian insulin cDNA" without more, is not an adequate written description of the genus because it does not distinguish the genus from others, except by function. It does not specifically define any of the genes that fall within its definition. It does not define any structural features commonly possessed

> by members of the genus that distinguish them from others. One skilled in the art therefore cannot, as one can do with a fully described genus, visualize or recognize the identity of the members of the genus. **A definition by function, as we have previously indicated, does not suffice to define the genus** (emphasis added), because it is only an indication of what the gene does, rather than what it is.

Id. At 1568, 43 USPQ2d at 1406. The court concluded that "naming a type of material generally known to exist, in the absence of knowledge as to what that material consists of, is not a description of that material." Id.

Finally, the court addressed the manner by which a genus of cDNAs might be described. "A description of a genus of cDNAs may be achieved by means of a recitation of a representative number of cDNAs, defined by nucleotide sequence, falling within the scope of the genus or of a recitation of structural features common to the members of the genus, which features constitute a substantial portion of the genus." Id.

The Federal Circuit has recently clarified that a DNA molecule can be adequately described without disclosing its complete structure. See Enzo Biochem, Inc. V. Gen-Probe Inc., 296 F.3d 1316, 63 USPQ2d 1609 (Fed. Cir. 2002). The Enzo court adopted the standard that □the written description requirement can be met by "show[ing] that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics ....i.e., complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed

correlation between function and structure, or some combination of such characteristics. " Id. At 1324, 63 USPQ2d at 1613 (emphasis omitted, bracketed material in original).

The inventions at issue in Lilly and Enzo were DNA constructs per se, the holdings of those cases are also applicable to claims such as those at issue here. A disclosure that does not adequately describe a product itself logically cannot adequately describe a method of using that product.

Thus, the instant specification may provide an adequate written description of an inhibitor of ANT-1, or a variant ANT-1 protein, or the signal pathway being activated by ANT-1, as per standards shown in the example of Lilly by structurally describing a representative number of inhibitor of ANT-1, or a variant ANT-1 protein, or the signal pathway being activated by ANT-1, or by describing "structural features common to the members of the genus, which features constitute a substantial portion of the genus." Alternatively, as shown in the example of Enzo, the specification can show that the claimed invention is complete "by disclosure of sufficiently detailed, relevant identifying characteristics, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics."

In this case, the specification does not describe an inhibitor of ANT-1, or a variant ANT-1 protein, or the signal pathway being activated by ANT-1 required to practice the claimed method in a manner that satisfies either the standards as shown in the example of Lilly or Enzo. The specification does not provide the complete structure of any inhibitor of ANT-1, other than cyclophilin D and bongkrekic acid, or any variant ANT-1

protein, or the proteins involved in the signal pathway being activated by ANT-1, nor any functional characteristics coupled with a known or disclosed correlation between structure and function. Although the specification discloses the ANT-1 inhibitors cyclophilin D and bongkrekic acid, this does not provide a description of that would satisfy the standard as shown in the example of Enzo.

The specification also fails to describe an inhibitor of ANT-1, or a variant ANT-1 protein, or the apoptosis-inducing signal pathway being activated by ANT-1, by the standards shown in the example in Lilly. The specification describes only the ANT-1 inhibitors cyclophilin D and bongkrekic acid. In addition, the specification does not describe any variant ANT-1, nor any proteins involved in the apoptosis-inducing signal pathway being activated by ANT-1.Therefore, it necessarily fails to describe a "representative number" of such species. In addition, the specification also does not describe "structural features common to the members of the genus, which features constitute a substantial portion of the genus."

It is noted that the recitation of two specific molecules, the ANT-1 inhibitors cyclophilin D and bongkrekic acid, would not be a representative number of species of substances that inhibit the activity of ANT-1, or of ANT-1 protein antagonists, because they do not share a common structural feature with each other, and because the specification does not disclose common structural features among the claimed ANT-1 inhibitors. A generic statement in the specification of a class of compounds with a common function, without disclosure of a representative number of species or common structural features among the claimed genus is not sufficient to meet the written

description requirement, and one would conclude that the claimed invention did not have possession of the claimed substances that inhibit the activity of ANT-1, or ANT-1 protein antagonists at the time the invention was made.

It is further noted that in a recent 2004 court case (*Rochester v. Searle*, 358 F.3d 916, Fed Cir., 2004) recited by Appellant, the court states that "even with the three dimensional of enzymes such as COX-1 and COX-2 in hand, it may even now not be within the ordinary skill in the art to predict what compounds might bind to and inhibit them".

The present application is similar to that in Rochester case, in that although the structure of ANT-1 is known in the art, one cannot predict what mimetics or what small molecule direct or indirect inhibitors that are capable of inhibiting the activity of ANT-1 in vivo, especially in view that three dimensional structure of ANT-1 is not even disclosed in the specification or known in the art.

Thus, the specification does not provide an adequate written description of an inhibitor of ANT-1, or a variant ANT-1 protein, or the signal pathway being activated by ANT-1 that is required to practice the claimed invention.

Since the specification fails to adequately describe the product for use in the claimed method, it also fails to adequately describe the claimed method.

REJECTION UNDER 35 USC 112, FIRST PARAGRAPH, ENABLEMENT

Claims 63-65, 69-75 rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which

was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Claims 63-65, 69-75 are drawn to:

1) A method for inhibition of apoptosis in a cell that could be associated with a pathogenic disorder, or treating diseases associated with excessive apoptosis, wherein the disease is a degenerative disease, and wherein said degenerative disease is dilated cardiomyopathy, comprising administering "a substance capable of inhibiting the activity of adenine nucleotide translocase-1 (ANT-1), or ANT-1 protein antagonists", or cyclophilin D (claims 63-65, 69-71, 73-75).

2) The method of claim 63, wherein an apoptosis-inducing signal transduction pathway is inhibited, said pathway being activated by ANT-1 (claim 72).

The specification discloses isolation and sequencing of a gene, which encodes the known protein ANT-1, the ADP/ATP translocator protein of the PT pore, as disclosed by Marzo et al, 1998b (p.11, last paragraph). There is no disclosure in the specification the actual amino acid sequence of ANT-1.

The specification discloses that the N-terminal half of ANT-1 is sufficient for apoptosis induction in a cell line (p.13, item 2.2). The specification discloses that cyclophilin D, when cotransfected with cyclophilin D, a PT pore component in a cell line, represses apoptosis induced by ANT-1.

The specification discloses that in dilated cardiomyopathy, there is a dramatic increase in the expression level of ANT-1 and excessive apoptosis induction (p.3, lines 13-16)

A. It is noted that ANT-1 an essential material for use in the claimed method. However, MPEP 6.19 teaches that incorporation of **essential material** in the specification by reference to a foreign application or patent, or to a publication is improper. Applicant is required to amend the disclosure to include the material incorporated by reference. The amendment must be accompanied by an affidavit or declaration executed by the applicant, or a practitioner representing the applicant, stating that the amendatory material consists of the same material incorporated by reference in the referencing application. In re Hawkins, 486 F.2d 569, 179 USPQ 157 (CCPA 1973); In re Hawkins, 486 F.2d 579, 179 USPQ 163 (CCPA 1973); In re Hawkins, 486 F.2d 577, 179 USPQ 167 (CCPA 1973) (see MPEP 6.19 and 6.19.01) .

Further, the use of **the language "adenine nucleotide translocase-1" (ANT-1) without being accompanied by a sequence identification number encompasses variant adenine nucleotide translocase-1 (ANT-1)** in view of the lack of a definition of ANT-1.

The specification describes ANT-1 as a central component of the permeability transition pore in mitochondria (p.1, lines 6-8).

It is noted that a component of the permeability transition pore could compose of a family of adenine nucleotide translocase-1.

Applicants have not shown how to make and use the claimed polypeptide ANT-1 variants which are capable of functioning as that which is being disclosed.

Protein chemistry is probably one of the most unpredictable areas of biotechnology. Bowie et al (Science, 1990, 257:1306-1310) teach that an amino acid sequence encodes a message that determines the shape and function of a protein and that it is the ability of these proteins to fold into unique three-dimensional structures that allows them to function and carry out the instructions of the genome and further teaches that the problem of predicting protein structure from sequence data and in turn utilizing predicted structural determinations to ascertain functional aspects of the protein is extremely complex. (col 1, p. 1306). Bowie et al further teach that while it is known that many amino acid substitutions are possible in any given protein, the position within the protein's sequence where such amino acid substitutions can be made with a reasonable expectation of maintaining function are limited. Certain positions in the sequence are critical to the three dimensional structure/function relationship and these regions can tolerate only conservative substitutions or no substitutions (col 2, p. 1306). The sensitivity of proteins to alterations of even a single amino acid in a sequence are exemplified by Burgess et al (J of Cell Bio. 111:2129-2138, 1990) who teach that replacement of a single lysine reside at position 118 of acidic fibroblast growth factor by glutamic acid led to the substantial loss of heparin binding, receptor binding and biological activity of the protein and by Lazar et al (Molecular and Cellular Biology, 1988, 8:1247-1252) who teach that in transforming growth factor alpha, replacement of aspartic acid at position 47 with alanine or asparagine did not affect biological activity

while replacement with serine or glutamic acid sharply reduced the biological activity of the mitogen. These references demonstrate that even a single amino acid substitution will often dramatically affect the biological activity and characteristics of a protein.

In view of the above unpredictability, one of skill in the art would be forced into undue experimentation in order to perform the claimed invention as broadly as claimed.

B. If Applicant could overcome the above 112, first paragraph rejection, claims 63-65, 69-75 are still rejected under 112, first paragraph, for lack of enablement for a method for "in vivo" inhibition of apoptosis in a cell, or of apoptosis in cells associated with a pathogenic disorder, or a method for treating a disease associated with excessive apoptosis, wherein said disease is a degenerative disease, and wherein said degenerative disease is dilated cardiomyopathy.

It is noted that a method for inhibition of apoptosis in a cell encompasses a method for in vivo inhibition of apoptosis.

One cannot extrapolate the teaching in the specification to the enablement of the claims.

Although cyclophilin D when transfected together with ANT-1 into a cell line could inhibit apoptosis induced by ANT-1, **one cannot predict that an inhibitor of ANT-1 or cyclophilin D would be effective in inhibiting apoptosis in vivo.** Apoptosis is a complex phenomenon, wherein there are diverse cell death pathways, which depend on cell type and cell death stimulus, and the concentration of proteins involved in the apoptosis pathway (Vogel MW et al, 2002, Cerbellum, 1(4): 277-87). For example, it is

well known in the art that the cellular concentration of members of Bcl-2 family is directly related to whether a cell will respond to an apoptotic signal, and that resistance of mature thymocytes to apoptotic signals correlates with high expression level of Bcl-2 protein, and overexpression of a cell death promoter BAD would counter the death inhibitory activity of Bcl-XL (Oltvai et al, 1994, Cell, 79: 189-192). Gottschalk, AR et al, 1996, Cell Death and Differentiation, 3(1): 113-118, teach that regulation of a cell's apoptotic threshold is likely to result from a complex set of interactions among Bcl-2 family members and other, as yet uncharacterized, regulators of apoptosis. Thus, it is clear that in vitro conditions cannot duplicate the complex conditions of the *in vivo* environment involved in cell-cell interactions, and homeostasis. In addition, Xu Xin et al, 2001, FASEB J, 15(4): A313, teach that compensatory mechanism could regulate apoptosis to overcome the low induction of Fas and FasL in activated CD4+ cells of IRF-1 null mice. Similarly, there exist apoptosis promoters in cells, that could counteract the effect of inhibition of apoptosis. For example, overexpression of BAR, a well known apoptosis promoter, can inhibit Bcl-2 from prolonging cell survival upon growth factor withdraw (Gottschalk, AR et al, 1996, Cell Death and Differentiation, 3(1): 113-118).

In view of the above teaching in the art, one cannot predict that the inhibition of apoptosis by an inhibitor of ANT-1 or cyclophilin D would not be encountered by apoptosis promoters in vivo, due to the well known homeostasis phenomena.

Further, **one cannot predict that dilated cardiomyopathy could be successfully treated using the claimed inhibitor of ANT-1 or cyclophilin D.**

It is well known in the art that **treatment of cardiomyopathy is unpredictable**. For example, James K B et al, Cardiovascular clinics,1989,19(3): p81-96 teach that peripartum cardiomyopathy, an idiopathic dilated cardiomyopathy associated with pregnancy is unpredictable, difficult to treat and incurable, and that these disorders carry on indefinitely for the duration of the patient life (p.87, paragraph under Peripartum cardiomyopathy, and p.94, under Summary) . James K B et al further teach that there is continuing controversy about the usefulness of digitalis for the treatment, and that more study is needed before we know the proper role for immunosuppressive therapy (p.89 last paragraph under Treatment, bridging p.90). Similarly, LaVecchia L et al, PACE, 1999, 22: 397-399, teach that for treatment of dilated cardiomyopathy, dobutamine infusion have contradictory results, and even with low dose of dobutamine, unpredictable fatal arrhythmia may occur (abstract and introduction on p.397).

. Further, a therapeutic agent must accomplish several tasks to be effective. It must be delivered into the circulation that supplies the heart and interact at the proper site of action and must do so at a sufficient concentration and for a sufficient period of time. In addition the target cell must not have a alternate means of survival despite action at the proper site for the drug. *In vitro* assays cannot duplicate the complex conditions of *in vivo* therapy. In the assays, the thereapeutic agent is transfected into the target cells, and thus overexpressed during the entire exposure period. This is not the case *in vivo*, where exposure tat the target site may be delayed or inadequate. In addition variables such as biological stability, half-life or clearance from the blood are important parameters in achieveing successful therapy. The peptide inhibitor may be

inactivated *in vivo* before producing a sufficient effect, for example, by proteolytic degradation, immunological activation or due to an inherently short half life of the protein and the *in vitro* tests of record do not sufficiently duplicate the conditions which occur *in vivo*. In addition, the inhibitor may not otherwise reach the targert because of its inability to penetrate tissues or cells where its activity is to be exerted, may be absorbed by fluids, cells and tissues where the polypeptide has no effect, circulation into the target area may be insufficient to carry the inhibitor and a large enough local concentration may not be established. The specification provides insufficient guidance with regard to theses issues and provides no working examples which would provide guidance to one skilled in the art and no evidence has been provided which would allow one of skill in the art to predict the efficacy of the claimed methods with a reasonable expectation of success.

In view of the above teaching in the art, one cannot predict that dilated cardiomyopathy could be successfully treated using the claimed inhibitor of ANT-1 or cyclophilin D.

Further, even if dilated cardiomyopathy could be treated using the claimed inhibitor of ANT-1 or cyclophilin, **one cannot predict that any disease associated with excessive apoptosis, or any degenerative disease could be successfully treated using the claimed inhibitor of ANT-1 or cyclophilin D**, because different diseases have different characteristics and properties, and do not necessarily have the same response to the same drug. For example, different cancers have different etiology and characteristics, and mutation or amplification of a gene in a specific cancer

is not necessarily the same as that for the same gene in another type of cancer. Montesano, R et al,1996, Intl J Cancer, 69(3): 225-235, teach that two different forms of esophagus cancer, squamous cell carcinoma (SCC) and adenocarcinoma (ADC) have different etiological and pathological characteristics, and that a comparison of p53 mutations in these two cancers shows that said mutations differ by their types, frequencies, distribution along the gene and impact on p53 protein structure (p.231, second column, first paragraph). Similarly, Burmer, GC et al, 1991, Environmental Health perspectives, 93: 27-31, teach that in contrast to sporadic colon carcinomas, mutations in c-Ki-ras are infrequently observed in carcinomas or areas of high-grade dysplasia in patients with chronic ulcerative colitis, and that differences in the frequency, and spectrum of mutations observed in sporadic colon carcinoma and pancreatic carcinoma suggest that a different class of carcinogens may be involved in the initiation of these two tumors (p.27, second column, last paragraph, bridging p.28). Busken, C et al, Digestive Disease Week Abstracts and Itinerary Planner, 2003, abstract No:850, teach that there is a difference in COX-2 expression with respect to intensity, homogeneity, localization and prognostic significance between adenocarcinoma of the cardia and distal esophagus, suggesting that these two cancers have different etiology and genetic constitution (last five lines of the abstract). Thus based on the teaching in the art and in the specification, one cannot predict that SEQ ID NO:9 is amplified in breast cancer.

In view of the above, it would be undue experimentation for one of skill in the art to practice the claimed invention.

Further not any disease associated with excessive apoptosis, or any degenerative disease would predictably have excess expression of ANT-1, due to the unpredictability of the expression level of a gene in a disease, and due to the fact that apoptosis regulation is complex and does not solely depend on the level of ANT-1. For example, Gottschalk, AR et al, 1996, Cell Death and Differentiation, 3(1): 113-118, teach that overexpression of BAR, a well known apoptosis promoter, although can inhibit Bcl-2 from prolonging cell survival upon growth factor withdraw, does not inhibit Bcl-XL from preventing apoptosis in a cell line WEHI-231. Gottschalk, AR et al further teach that regulation of a cell's apoptotic threshold is likely to result from a complex set of interactions among Bcl-2 family members and other, as yet uncharacterized, regulators of apoptosis.

In view of the above, it would be undue experimentation for one of skill in the art to practice the claimed invention.

C. If Applicant could overcome the above 112, first paragraph rejection, and even if cyclophilin D could inhibit apoptosis in vivo or could be used for treating dilated cardiomyopathy, claims 63-65, 69-70, 72-75 are still rejected under 112, first paragraph, for lack of enablement for a method for inhibition of apoptosis, or a method for treating a disease associated with excessive apoptosis, wherein said disease is a degenerative disease, and wherein said degenerative disease is dilated cardiomyopathy, using "a substance capable of inhibiting the activity of ANT-1 or ANT-1 protein antagonist".

It is noted that **an inhibitor of the activity of ANT-1, or an antagonist of ANT-1 encompasses both direct and indirect inhibitors of ANT-1, with diverse and unknown structure**, such as mimetics or small molecule inhibitors of ANT-1, or molecules that interfere with the protein-protein interaction by ANT-1 leading to apoptosis, or with the signal pathway being activated by ANT-1.

One cannot extrapolate the teaching in the specification to the scope of the claims, because one does not know how to make the broadly claimed inhibitor of ANT-1.

In a recent 2004 court case (*Rochester v. Searle*, 358 F.3d 916, Fed Cir., 2004) recited by Appellant, the court states that "even with the three dimensional of enzymes such as COX-1 and COX-2 in hand, it may even now not be within the ordinary skill in the art to predict what compounds might bind to and inhibit them".

The present application is similar to that in Rochester case, in that although the structure of ANT-1 is known in the art, one cannot predict what mimetics or what small molecule direct or indirect inhibitors that are capable of inhibiting the activity of ANT-1 **in vivo**, especially in view that three dimensional structure of ANT-1 is not even disclosed in the specification or known in the art.

Further, **an inhibitor of the activity of ANT-1 encompasses an inhibitor of the ADP/ATP exchange activity of ANT-1**. One cannot predict that an inhibitor of the ADP/ATP exchange activity of ANT-1 could be used for inhibiting of apoptosis, in view of the disclosure in the specification that ANT-1 apoptosis activity does not depend on its known function for ADP/ATP exchange (p.2, lines 29-31).

In view of the above, it would be undue experimentation for one of skill in the art to practice the claimed invention.

D. If Applicant could overcome the above 112, first paragraph rejection, claim 72 is still rejected under 112, first paragraph, for lack of enablement for a method for inhibition of apoptosis, wherein an apoptosis-inducing signal pathway is inhibited, said pathway is being activated by ANT-1.

The specification does not discloses which apoptosis-inducing signal pathway is activated by ANT-1.

In view of a lack of a knowledge of which apoptosis-inducing signal pathway is activated by ANT-1, and the proteins involved in said signal pathway, and in view that apoptosis is a complex phenomenon, wherein there are diverse cell death pathways, which depend on cell type and cell death stimulus (Vogel MW et al, 2002, Cerbellum, 1(4): 277-87), one would not know how to make an inhibitor for the apoptosis-inducing pathway that is activated by ANT-1, such that apoptosis would be inhibited.

In view of the above, it would be undue experimentation for one of skill in the art to practice the claimed invention.

REJECTION UNDER 35 USC 102(b)

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 63-65, 69-70, 72 are rejected under 35 U.S.C. 102(b) as being anticipated by Fulda et al, Cancer res, 1998, 58(19): 4453-60, of record.

Claims 63-65, 69-70, 72 are drawn to:

1) A method for inhibition of apoptosis in a cell, wherein said cell could be associated with a pathogenic disorder, comprising administering "a substance capable of inhibiting the activity of adenine nucleotide translocase-1 (ANT-1), or ANT-1 protein antagonists" (claims 63-65, 69-70)

2) The method of claim 63, wherein an apoptosis-inducing signal transduction pathway is inhibited, said pathway being activated by ANT-1 (claim 72).

Fulda et al teach apoptosis in neuroblastoma cells is inhibited by bongkreric acid, an agent that stabilizes mitochondria membrane barrier function (abstract).

The method taught by Fulda et al seems to be the same as the claimed method, in view that bongkreric acid is an inhibitor of ANT-1, as taught by Pei, Y Z et al, 2003, Synthesis-Stuttgart, 11, SI: 1717-1721, of record.

Further, although Fulda et al do not teach that an apoptosis-inducing signal transduction pathway is inhibited, said pathway being activated by ANT-1, the claimed method seems to be the same as the method taught by Fulda et al, in view that the method of the prior art comprises the same method steps as claimed in the instant invention using the same composition.

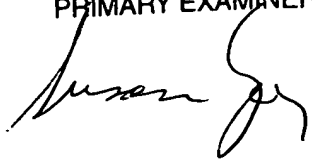
Because the method of the prior art comprises the same method steps as claimed in the instant invention using the same composition, the claimed method is anticipated because the method will inherently lead to the claimed effects. See Ex parte Novitski 26 USPQ 1389 (BPAI 1993).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to MINH-TAM DAVIS whose telephone number is 571-272-0830. The examiner can normally be reached on 9:00 AM-5:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, JEFFREY SIEW can be reached on 571-272-0787. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

SUSAN UNGAR, PH.D
PRIMARY EXAMINER



MINH TAM DAVIS

August 30, 2005